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Metabolic Factors Modulating the Connection Between Diabetes and Pulmonary Alterations

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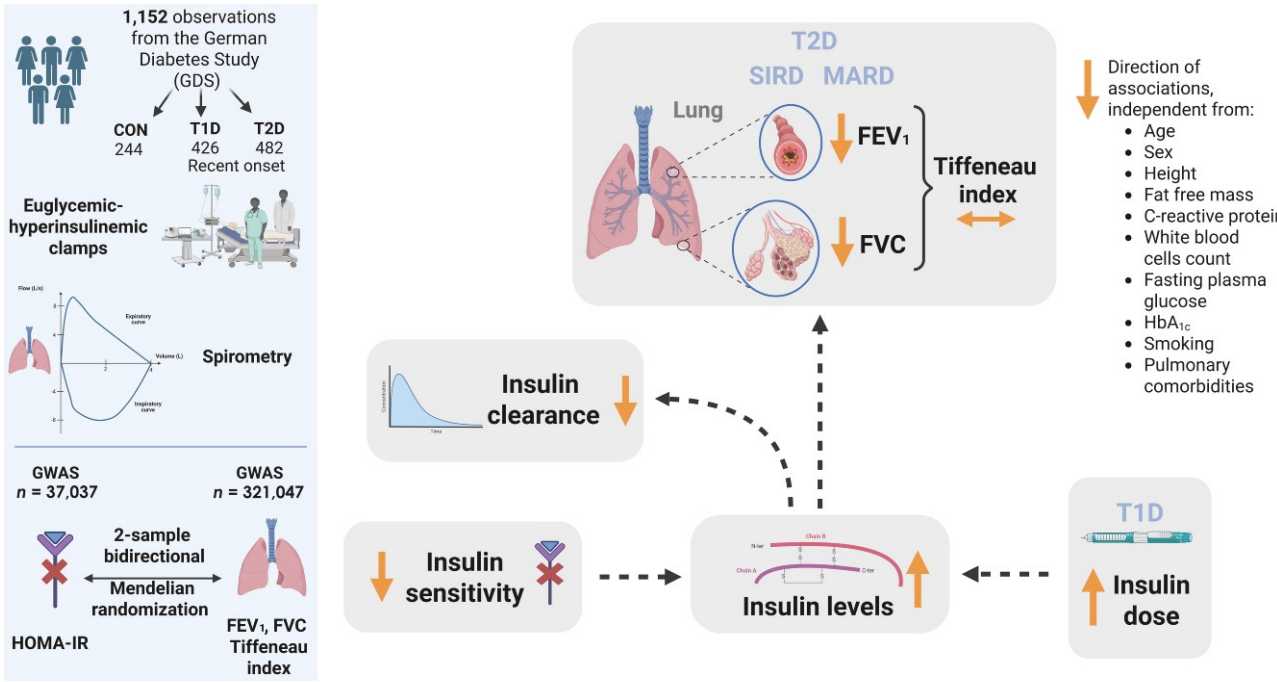

CON, normal glucose tolerance as the control; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GWAS, genome-wide association study; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostasis model assessment insulin resistance; MARD, mild age-related diabetes; SIRD, severe insulin-resistance diabetes; T1D, Type 1 diabetes; T2D, Type 2 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Both type 1 and type 2 diabetes are associated with restrictive pulmonary alterations, but the responsible glucometabolic mechanisms are unknown.

- **What is the specific question we wanted to answer?**
  Is insulin resistance, insulin secretion, or insulin clearance the key mechanism behind pulmonary alterations?

- **What did we find?**
  Lower forced expiratory volume in 1 s and forced vital capacity in diabetes associate with whole-body insulin resistance, impaired insulin clearance, and, in type 1 diabetes, with higher insulin doses independent from confounders.

- **What are the implications of our findings?**
  Individuals at risk for pulmonary complications may benefit from early screening and targeted interventions aimed at enhancing insulin sensitivity and lowering hyperinsulinemia to help prevent negative pulmonary outcomes.

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Metabolic Factors Modulating the Connection Between Diabetes and Pulmonary Alterations

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OBJECTIVE

Type 1 and 2 diabetes have been variably associated with reduced forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), but mechanisms remain unclear. This study examined the role of glucose and insulin metabolism for pulmonary function across diabetes (sub)types and normal glucose tolerance as the control (CON) in the German Diabetes Study (GDS) and assessed causality by Mendelian randomization (MR) analyses in independent cohorts.

RESEARCH DESIGN AND METHODS

In GDS, 426 spirometry measurements of participants with type 1 diabetes, 482 of participants with type 2 diabetes, and 244 of CON were cross-sectionally analyzed after phenotyping, including Botnia clamps for insulin sensitivity (M value), secretion, and clearance. Associations between metabolic measures and lung function were assessed using generalized linear models, adjusting for confounders. MR analysis used data from the MAGIC (Meta-Analyses of Glucose and Insulin-Related Traits Consortium) consortium (HOMA-insulin resistance [IR], n = 37,037) and the UK Household Longitudinal Study (pulmonary function, n = 321,047).

RESULTS

In GDS, higher M value (all $\beta > 0.18$, $P < 0.0001$) and insulin clearance (all $\beta = 0.05$, $P < 0.050$) were associated with higher FEV_1 and FVC. Compared with type 1 diabetes and CON, type 2 diabetes had lower FEV_1 and FVC, which associated with M value (all $\beta > 0.17$, $P < 0.050$). FEV_1 was associated with daily insulin doses in type 1 diabetes ($\beta = -0.21$, $P = 0.0006$). FEV_1 was associated with type 2 diabetes ($\beta = -0.19$, $P = 0.0052$), severe insulin resistant ($\beta = -0.27$, $P = 0.039$), and mild age-related diabetes ($\beta = -0.23$, $P = 0.0033$). MR supported a causal association between HOMA-IR and lower FEV_1 ($\beta = -0.13$, $P = 0.0018$).

CONCLUSIONS

Lower FEV_1 and FVC in diabetes are linked to insulin resistance, impaired clearance, and higher insulin doses, all of which result in higher insulinemia and likely represent underlying pathogenic mechanisms.

Diabetes and pulmonary diseases increasingly contribute to the global burden of chronic health conditions, raising significant public health concerns (1). Beyond established cardiovascular complications, genetic evidence suggests a link between glycemia and pulmonary impairment, indicating that higher glucose levels are associated with impairment of lung function (2). Furthermore, the lung has been shown to be a possible target organ for diabetes-related complications (3,4), and diabetes has

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*A complete list of the German Diabetes Study group can be found in the supplementary material online.

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been associated with increased risk of pulmonary diseases, such as chronic obstructive pulmonary disease (COPD; hazard ratio [HR] 1.22) and pneumonia (HR 1.92) (5). Diabetes also increases the risk of interstitial lung disease, particularly pulmonary fibrosis, to a magnitude similar to that of smoking, and is associated with breathlessness (6,7).

Type 1 and type 2 diabetes have both been variably associated with a reduction of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) compared with normal glucose tolerant individuals (8,9). Type 2 diabetes was associated with obstructive ventilation pattern, even in newly diagnosed individuals (10). Different processes have been proposed to explain the pathophysiology of pulmonary function alterations in diabetes, such as hyperglycemia (11), insulin resistance (12), autonomic neuropathy (13), angiopathy of alveolar capillaries and pulmonary arterioles (14), alterations in respiratory muscle function (15,16), and persisting DNA damage signaling due to reactive oxygen species leading to cells senescence, proinflammatory cytokines secretion, and fibrosis (17). However, mechanisms connecting pulmonary alterations and dysglycemia are unclear because large studies using in-depth metabolic phenotyping are missing. Furthermore, pulmonary function alterations in diabetes have been associated with the presence of diabetes-related comorbidities, such as chronic kidney disease, and with increased mortality risk (18,19).

Diabetes is recognized as a heterogeneous disease with five phenotype-based subtypes in adult age that carry different risks for diabetes progression and comorbidities (20,21). The analysis of these different subtypes, which likely represent distinct pathogenic mechanisms, may provide insights into the connection between diabetes and pulmonary impairment.

This study aims to precisely investigate which glucose metabolism traits associate with pulmonary function changes in a comprehensively phenotyped cohort (German Diabetes Study [GDS]) comprising individuals with recent-onset type 1 and type 2 diabetes, as well as normal glucose-tolerant individuals. Furthermore, to test whether there is a causal association between insulin resistance and pulmonary alterations, a Mendelian randomization (MR) analysis was performed in GDS independent cohorts.

RESEARCH DESIGN AND METHODS

Study Participants

From the ongoing GDS, all participants with available spirometry data, including follow-up examinations, were included in this study. The study design and cohort profile of the GDS are described elsewhere in detail (22). All participants gave written informed consent before inclusion in the study (ClinicalTrials.gov registration no. NCT01055093), which was performed according to the Declaration of Helsinki and its latest 2013 amendment and approved by the Heinrich Heine University Institutional Review Board, Düsseldorf, Germany. Exclusion criteria were known duration of diabetes >1 year, poor glycemic control, glycosylated hemoglobin (HbA_{1c}) >9.0% (75 mmol * mol^{-1}), or severe acute or chronic disease. Participants suspended their oral glucose-lowering medication for at least 3 days before all measurements and their insulin treatment according to drug duration of action to exclude pharmacological effects on glucose metabolism.

Study Protocol

All participants arrived at the Clinical Research Centre in the morning after a 10-h overnight fast. On the first day, medical history was recorded, in addition to bioimpedance analysis to compute fat-free mass (FFM) and fat mass as well as physical and laboratory examinations, spirometry, and cycling spiroergometry. All participants without a diagnosis of diabetes underwent a 75-g oral glucose tolerance test (Accu-Chek Dextro O.G–T., Roche, Basel, Switzerland). On the second day, a modified Botnia clamp test was performed. On the third day, ^{1}H MRS/MRI measurements were performed (22). For 3 days prior to each visit, participants refrained from physical activity and alcohol ingestion and adhered to a balanced isocaloric diet.

Laboratory Analyses

Fasting plasma glucose (FPG), insulin, C-peptide, HbA_{1c}, HDL- and LDL-cholesterol, triglycerides, hs-CRP, and white blood count (WBC) were measured in the fasted state, as previously described (22).

Lung Function Tests

A spirometry was performed (Jaeger Vyntus CPX, Care Fusion Germany 234 GmbH, Hoechberg, Germany), assessing *1*) FEV_1 as an absolute value and as a percentage of predicted (FEV_1%) for age, sex, height, and ethnicity; *2*) FVC as an absolute value and as a percentage of predicted (FVC%); *3*) the FEV_1-to-FVC ratio (Tiffeneau index); and *4*) peak expiratory flux (PEF). FEV_1 is the air forcefully exhaled in the first second, with lower values primarily indicating an obstruction of air passage. FVC represents the total amount of air forcefully exhaled after taking a deep breath, indicating lungs' expansion and contraction capacity as well as the total amount of air they can hold. The Tiffeneau index provides insights into potential obstructions or limitations in the airways. PEF is the maximum speed at which a person can exhale air during a forced breath, providing information about the function of large airways. All of the measurements were performed at least three times by a medical professional. The best FEV_1 value, alongside other measures from the same set, was taken into account for the analysis. Since the study population comprises people of White European ancestry, FEV_1% and FVC% were calculated with the Global Lung Function Initiative (GLI) 2012 equations, which are recognized as suitable for this population (23). FEV_1% and FVC% were also computed with the new race-neutral GLI 2022 equations alongside with the *Z* scores of FEV_1 and FVC in relation to predicted values (24). All computations were performed with the package "rspiro" using R 4.4.1 software (R Core Team).

Botnia Clamp Test

All participants underwent a Botnia clamp test starting with an intravenous glucose tolerance test (ivGTT), followed by the hyperinsulinemic-euglycemic clamp. For the latter procedure, a priming dose (10 mU * body weight [kg]$^{-1}$ * min^{-1} for 10 min), followed by a continuous infusion of short-acting human insulin (Insuman Rapid, Sanofi, Frankfurt am Main, Germany) (1.5 mU * body weight [kg]$^{-1}$ * min^{-1}) for 3 h was used to assess whole-body insulin sensitivity with space correction (M value). Variable intravenous infusion of 20% glucose is adjusted to maintain blood glucose concentration at 90 mg/dL. In detail, M value without space correction is computed with the following equation:

$$(\text{GIR}\ [mL/h]\ *\ 200\ [mL/h])/$$

$$(\text{body weight}\ [\text{Kg}]\ *\ 60\ [\text{min}/h])$$

where GIR is the mean glucose infusion rate at steady-state. Then, space correction is calculated as:

$$(\mathrm{BG_{END}}[\mathrm{mg}/dL] - \mathrm{BG_{BEGIN}}[\mathrm{mg}/dL]) * 1.9[dL/\mathrm{kg}]/\Delta t,$$

where $\mathrm{BG_{END}}$ and $\mathrm{BG_{BEGIN}}$ are blood glucose at the end and beginning of steady-state and Δt is the duration of steady-state. Finally, the M value with space correction is computed subtracting space correction from the M value without space correction. During the clamp test, insulin clearance, which represents the uptake and degradation of insulin in the insulin-sensitive tissues, was assessed as previously described (25). In particular, it was calculated during clamp steady-state with the following equation:

$$(I_i[\mathrm{mU} * \mathrm{Kg} * \mathrm{min}^{-1}] + \mathrm{EI})/I_{SS}[\mathrm{mU} * \mathrm{min}^{-1}],$$

where I_i is the insulin infusion rate, EI is the residual endogenous insulin secretion rate, and I_{SS} is clamp steady-state plasma mean insulin levels measured from 200 to 240 min. The EI was calculated as follows:

$$\mathrm{Insulin_0} * \mathrm{C} - \mathrm{peptide_{clamp}}/\mathrm{C} - \mathrm{peptide_{fasting}},$$

where $\mathrm{insulin_0}$ is insulin levels at the beginning of the clamp test. To assess insulin secretion, area under the curve (AUC) of blood insulin concentrations on the first 10 minutes of the ivGTT was computed (ivGTT-$\mathrm{AUC_{0–10}}$Ins).

Diabetes Subtypes

For participants with available baseline data, we applied the centroid approach for diabetes cluster classification from baseline variables using a validated online clustering algorithm (www.diabetescalculator.ddz.de) (20,21,26). Individuals were assigned to severe autoimmune diabetes (SAID), mild age-related diabetes (MARD), mild obesity-related diabetes (MOD), severe insulin-resistant diabetes (SIRD), or severe insulin-deficient diabetes (SIDD).

Statistical Analyses

Sample size calculation was based on detecting a difference in $\mathrm{FEV_1}$ between participants with type 2 diabetes and individuals with normal glucose tolerance as controls (CON), using sex-weighted means and SDs from Yeh et al. (3). The estimated effect size (Cohen *d*) was 0.285, based on a mean difference of 0.164 L and a pooled SD of 0.575 L. Assuming a two-sided α of 0.05 and 80% power, 195 observations per group were required. Baseline characteristics were compared through ANOVA, Kruskal-Wallis, or χ^2 test. For the analysis of repeated-measures data, generalized linear mixed models (GLMMs) were used. GLMMs assessed effects of diabetes (sub)types on pulmonary function, adjusting for age, sex, height, BMI, smoking status, history of asthma/COPD/inhaled drugs use, and visit. GLMMs were fitted both in the whole population, as well as separately for type 1 and type 2 diabetes, further adjusting for FFM (instead of BMI), hsCRP, WBC, and history of cardiovascular disease. In the subgroup analysis in both type 1 and type 2 diabetes, known diabetes duration was included (instead of visit). Total daily insulin dose (sum of rapid-acting and basal insulin) and fasting insulinemia were included among glucose metabolism traits, in type 1 and type 2 diabetes, respectively. In all GLLMs, participant was treated as random effect. Multicollinearity was checked via variance inflation factor (VIF). All statistical tests were two-sided, and a $P < 0.05$ was considered significant. Statistical analyses were performed, and graphs were generated using R 4.4.1 (R Core Team).

Bidirectional MR Analysis

To evaluate causal association between insulin resistance (in genome-wide association studies measured with HOMA insulin resistance [IR], data from UK Household Longitudinal Study) and lung function (FEV1, FVC, and Tiffeneau index, data from Meta-Analyses of Glucose and Insulin-Related Traits Consortium [MAGIC]), a bidirectional two-sample MR analysis was conducted using single nucleotide polymorphisms (SNPs) as instrumental variables (27). Inverse-variance weighted (IVW) analysis was selected as primary method (28). Detailed information about the MR analysis is provided in Supplementary Fig. 1 and Supplementary Table 1.

Data and Resource Availability

The data sets generated or analyzed during the current study are not available publicly because they are subject to national data protection laws and restrictions imposed by the ethics committee to ensure privacy of study participants. However, pseudonymized data can be requested through an individual project agreement with the principal investigator of the GDS. The study protocol and the individual methods have been published in the cohort profile (22) and are unrestrictedly available.

RESULTS

Participants' Characteristics

From the GDS cohort, 339 individuals with recent-onset type 1 diabetes (426 spirometry measurements), 403 individuals with recent-onset type 2 diabetes (482 spirometry measurements), and 188 CON participants (244 spirometry measurements) were included. Characteristics of the study population according to diabetes type are reported in Table 1, whereas in the Supplementary Table 2, population was stratified according to diabetes subtype. Individuals with type 2 diabetes showed higher prevalence of pulmonary comorbidities than CON and had higher prevalence of cardiovascular disease compared with participants with type 1 diabetes. Individuals with type 2 diabetes had more frequent use of antihypertensive medication and acetylsalicylic acid compared with both type 1 diabetes and CON. A higher percentage of people with type 1 and type 2 diabetes received statins compared with CON. Participants with type 2 diabetes tended to use more inhaled medication (i.e., inhaled corticosteroids, β_2-receptor agonists, and muscarinic-receptors antagonists) compared with all other groups (Supplementary Table 3). Medication of the study population stratified by diabetes subtypes is shown in Supplementary Table 4.

Pulmonary Function Across Individuals With and Without Diabetes

Individuals with type 2 diabetes showed a lower $\mathrm{FEV_1}$ and FVC than CON and individuals with type 2 diabetes. The study groups did not differ for the Tiffeneau index (Supplementary Table 5). Additionally, participants with type 2 diabetes exhibited a lower PEF compared with both CON and type 1 diabetes. There was also a trend toward lower $\mathrm{FEV_1}$% in individuals with type 2 diabetes compared with CON, while FVC% was similar across the study groups when computed with the GLI 2012 equations (Supplementary Table 5). When *Z* scores were computed with the updated GLI 2022 equations, $\mathrm{FEV_1}$ and FVC both showed a trend toward lower *Z* scores in participants with type 2 diabetes (Fig. 1 and Supplementary

Table 1—Characteristics of the study population

	CON	Type 1 diabetes	Type 2 diabetes	*P* value
	(*n* = 188)	(*n* = 339)	(*n* = 403)	—
Age, years	43.77 ± 14.17	40.92 ± 12.68*	55.80 ± 10.28*†	<0.0001
Sex				
Male	118 (62.8)	195 (57.5)	260 (64.5)	0.14
Female	70 (37.2)	144 (42.5)	143 (35.5)	
Height, cm	175.86 ± 9.53	175.23 ± 9.44	173.23 ± 9.45*†	0.0014
BMI, kg/m^2	26.65 ± 4.79	26.05 ± 4.91	31.50 ± 6.19*†	<0.0001
FFM, kg	59.22 ± 11.94	58.07 ± 11.80	60.73 ± 11.48†	0.0085
Fat mass, kg	23.61 ± 10.48	22.15 ± 10.20	33.81 ± 12.52*†	<0.0001
Waist, cm	90.97 ± 14.95	88.99 ± 15.08	105.66 ± 14.80*†	<0.0001
Hip, cm	102.69 ± 11.18	101.42 ± 10.84	110.06 ± 12.86*†	<0.0001
Smoking status				0.0051
Never smokers	99 (52.7)	178 (52.5)	166 (41.2)*†	—
Former smokers	53 (28.2)	94 (27.7)	157 (39.0)*†	—
Current smokers	36 (19.1)	67 (19.8)	80 (19.9)	—
Asthma/COPD/inhaled drugs‡	9 (4.8)	31 (9.1)	46 (11.4)*	0.035
Cardiovascular disease	8 (4.3)	12 (3.5)	31 (7.7)†	0.030
Known diabetes duration, years	—	3.81 ± 3.53	4.20 ± 3.63	0.13
FPG, mg/dL	82.32 ± 5.96	138.13 ± 40.03*	138.81 ± 45.38*	<0.0001
Fasting insulin, mU/L	6.50 (3.90, 9.60)	8.50 (3.92, 21.35)*	15.10 (8.60, 23.80)*†	<0.0001
Fasting C-peptide, ng/mL	1.57 (1.13, 2.11)	0.50 (0.16, 1.11)*	2.87 (2.11, 4.04)*†	<0.0001
HbA_{1c}, %	5.19 ± 0.29	6.79 ± 0.99*	6.77 ± 1.07*	<0.0001
HbA_{1c}, mmol/mol	33.20 ± 3.21	50.75 ± 10.83*	50.51 ± 11.72*	<0.0001
M value, mg/(kg * min)	10.82 ± 3.42	7.44 ± 3.15*	5.95 ± 2.53*†	<0.0001
ivGTT-$AUC_{0\text{-}10}$ Ins	305.90 (186.59, 505.72)	68.93 (23.48, 174.17)*	139.18 (70.59, 226.34)*†	<0.0001
Insulin clearance, a.u.	0.07 (0.05, 0.08)	0.07 (0.05, 0.09)	0.07 (0.06, 0.08)	0.21
hs-CRP, mg/dL	0.09 (0.05, 0.18)	0.12 (0.06, 0.28)*	0.20 (0.10, 0.40)*†	<0.0001
WBC, /µL	5,921.89 ± 1,558.70	5,998.72 ± 1,702.04	6,927.93 ± 1,686.62*	<0.0001

Data are shown as mean ± SD, median (first, third quartile), or absolute numbers (%). *P* values are computed through ANOVA with Tukey post hoc test for pairwise comparisons, Kruskal-Wallis with Dunn post hoc test for pairwise comparisons or χ^2 with post hoc Fisher test for pairwise comparisons as appropriate. Data are shown for the first visit time point available for each participant. BMI, FFM, fat mass, HbA_{1c}, FPG, M value, insulin secretion as area under the curve in the first 10 min of intravenous glucose tolerance test (ivGTT-$AUC_{0\text{–}10}$Ins), insulin clearance during clamp test, hs-CRP, and WBC were analyzed in fasted state. a.u. arbitrary unit ‡Asthma and/or COPD and/or inhaled drugs history. *P value < 0.05 vs. CON. †P value < 0.05 vs. T1D.

Table 5). After adjusting for confounders, such as age, sex, height, BMI, smoking status, pulmonary comorbidities, and visit, FEV_1 (Supplementary Table 6) but not FVC (Supplementary Table 7) was lower for participants with type 2 diabetes compared with CON. When therapy with metformin, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, or insulin was separately adjusted for in the model, lower FEV_1 remained significantly associated with type 2 diabetes. After adjusting for confounders, PEF was lower in participants with type 1 or type 2 diabetes (Supplementary Table 8).

Lung Function in Diabetes Subtypes

FEV_1 was lower in participants with SIRD, MARD, and MOD compared with CON and individuals with SAID, and lowest in those with SIRD (Supplementary Table 9). Similarly, FVC was reduced in participants with SIRD, MARD, and MOD again lowest in those with SIRD (Supplementary Table 9). In Fig. 1, *Z* scores for FEV_1 and FVC across diabetes subtypes computed with GLI 2022 equations are represented. After adjusting for confounders, such as age, sex, height, BMI, smoking status, pulmonary comorbidities, and visit (Supplementary Tables 10–12), SIRD and MARD were associated with lower FEV_1 and PEF, but not FVC. The impact of allocation to SIRD or MARD on FEV_1 was larger than the effect of being diagnosed with unspecified type 2 diabetes (Supplementary Table 13). In particular, it was highlighted that unspecific type 2 diabetes, SIRD, and MARD accounted for a 5.8%, 7.3%, and 6.4% mean reduction in FEV_1, respectively.

Associations of Lung Function With Key Traits of Glucose Metabolism

After adjusting for confounders, such as age, sex, height, FFM, hsCRP, WBC, smoking status, pulmonary comorbidities, history of cardiovascular disease, and visit (Supplementary Tables 14, 15, and 16),

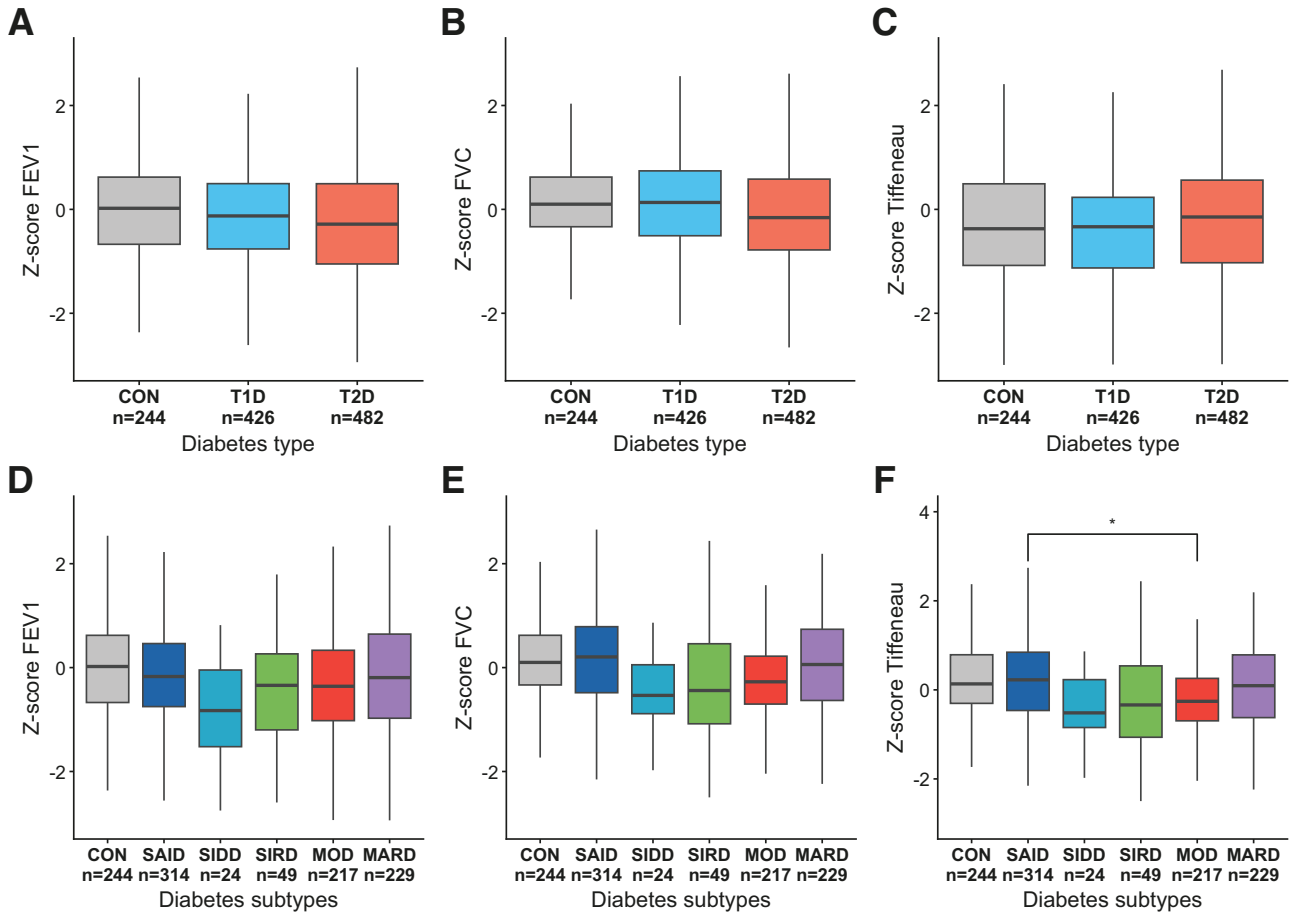

Figure 1—Box plots show principal pulmonary function test results across diabetes type and diabetes subtypes. The number on the *x*-axis under every box plot represents the total number of measurements. *Z* scores for FEV_1 (*A*), for FVC (*B*), and for the Tiffeneau index (FEV_1-to-FVC ratio) (*C*) across diabetes types. *Z* scores for FEV_1 (*D*), for FVC (*E*), and for the Tiffeneau index (*F*) across diabetes subtypes. T1D, type 1 diabetes; T2D, type 2 diabetes.*$P < 0.05$. Data were compared by GLMMs with Tukey post hoc test for pairwise comparisons. *Z* scores were computed with the Global Lung inititiative 2022 equations (24).

both FEV_1 and FVC were associated with M value and insulin clearance (Fig. 2), whereas PEF was associated only with M value. Furthermore, FEV_1 was inversely associated with hsCRP, while FEV_1, FVC, and PEF were all positively correlated with FFM. No associations were found between lung function and insulin secretion, HbA_{1c}, or FPG. When participants with pulmonary comorbidities were excluded from the analyses, the association of FEV_1 and FVC with M value and insulin clearance remained significant.

Lung Function and Key Traits of Glucose Metabolism Across Diabetes Types

Type 1 diabetes, in contrast to type 2 diabetes, exhibited a trend toward a negative interaction effect on the relationship between M value and both FEV_1 (coefficient = −0.14, $P = 0.052$) and FVC (coefficient = −0.15, $P = 0.084$), reflecting an attenuation of the effect size of insulin sensitivity on the pulmonary outcomes. In individuals with type 1 diabetes (Supplementary Tables 17 and 18), both FEV_1 and FVC were associated with insulin clearance, and there was a trend for association with M value. PEF (Supplementary Table 19) was associated with M value but not with insulin clearance. Additionally, FEV_1 (Supplementary Fig. 2) and PEF were inversely associated with total daily insulin dose, and FEV_1 was inversely associated also with HbA_{1c}, while the association with hs-CRP was no longer present. FEV_1 was still correlated to FFM. Neither FEV_1 nor FVC were associated with diabetes duration in type 1 diabetes. In individuals with type 2 diabetes (Supplementary Tables 20–22), FEV_1, FVC, and PEF were all correlated with M value and insulin clearance as in the overall population. Furthermore, FEV_1, FVC, and PEF were not correlated with fasting insulin, while both FEV_1 and PEF were still positively associated with FFM, but FEV_1 was no longer associated with hsCRP. As for type 1 diabetes, neither FEV_1 nor FVC were associated with known diabetes duration.

Causal Association Between Insulin Resistance and Lung Function

We performed MR analyses to investigate whether insulin resistance is causally associated with pulmonary traits. HOMA-IR was causally associated with FEV_1 and FVC, but not with the Tiffeneau index. In the IVW analysis, FVC had a causal effect on HOMA-IR, while FEV_1 and the Tiffenau index did not (Table 2). Detailed information on SNPs is shown in Supplementary Tables 23 and 24. These findings were supported by the sensitivity analyses (Supplementary Table 25 and 26). The leave-one-out analysis revealed that the IVW estimates for HOMA-IR on FEV_1 and the Tiffeneau index, as well as for the

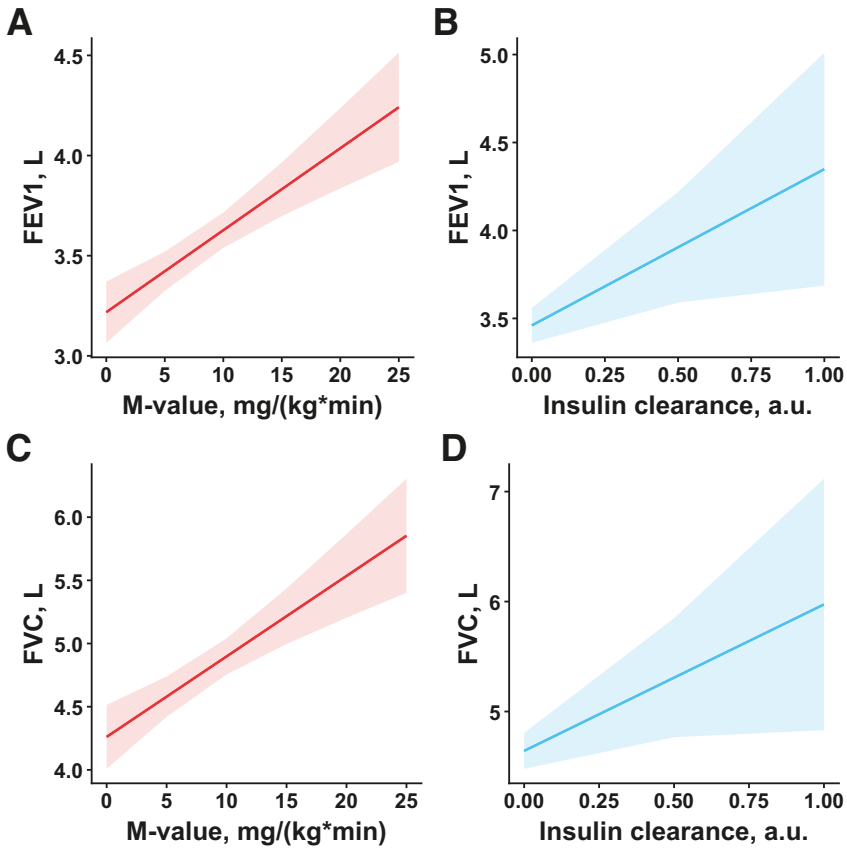

Figure 2—Predicted values of lung function measures according to variations in glucose metabolism traits, as estimated by GLMMs in the whole population. The graphs show the predicted values (lines) and confidence band (shaded areas) of lung function measures according to variations of glucose metabolism features estimated by GLMMs, with FEV_1 or FVC as the dependent variable, participant as random effect variable, and age, sex, height, FFM, M value, insulin clearance, insulin secretion, hs-CRP, WBC, fasting plasma glucose, HbA_{1c}, smoking status, asthma and/or COPD and/or inhaled drugs history, cardiovascular disease, and visit as explanatory variables. *A*: On the *x*-axis whole-body insulin sensitivity (M value); on the *y*-axis predicted values of FEV_1. *B*: On the *x*-axis insulin clearance; on the *y*-axis predicted values of FEV_1. *C*: On the *x*-axis whole-body insulin sensitivity (M value); on the *y*-axis predicted values of FVC. *D*: On the *x*-axis insulin clearance; on the *y*-axis predicted values of FVC. a.u., arbitrary unit.

Tiffeneau index on HOMA-IR, were robust. However, the estimates for HOMA-IR on FVC, as well as for FVC and FEV_1 on HOMA-IR, were influenced by single SNPs (Supplementary Tables 27 and 28). Therefore, these IVW results should be interpreted with caution.

CONCLUSIONS

This study revealed statistically lower FEV_1, FVC, and PEF in individuals with type 2 diabetes compared with those with type 1 diabetes and CON. Notably, FEV_1 reflects airway resistance, whereas FVC indicates the lung's overall capacity to expand. Reduced FEV_1 and FVC are usually observed in conditions such as interstitial lung diseases (e.g., pulmonary fibrosis), obesity, pulmonary edema, and pleural effusions. We expand this knowledge by demonstrating the presence of lower FEV_1, FVC, and PEF in the SIRD and MARD subtypes. The impact of type 2 diabetes, MARD, and SIRD on FEV_1 and PEF was independent from demographic and anthropometric factors, smoking status, inflammation, and pulmonary comorbidities. Furthermore, our results highlight whole-body insulin sensitivity and clearance, but not β-cell function, being linked to pulmonary function. The gold standard measures applied in the GDS validate results from previous studies using surrogate markers of insulin resistance such as HOMA-IR (12,29). Surrogate indices are limited by their partial ability to disentangle insulin sensitivity from insulin secretion and because they cannot be applied in individuals with reduced β-cell function or in those undergoing insulin therapy (30). In addition, the complementary MR analysis suggests a causal effect of insulin resistance on reduction of FEV_1 and FVC. Hyperinsulinemia, as a compensatory response to insulin resistance, is a hallmark of type 2 diabetes. While insulin resistance can also occur in type 1 diabetes, advanced β-cell dysfunction limits adaptive insulin secretion, decoupling these traits. In type 1 diabetes, after adjusting for confounders, higher total daily insulin dose rather than insulin sensitivity was associated with lower FEV_1. Additionally, insulin clearance was linked to FEV_1, suggesting that lower peripheral insulin levels are associated with higher FEV_1. These findings, combined with the lack of an association of inflammation with the pulmonary outcomes in multivariable models, suggest that peripheral hyperinsulinemia may drive pulmonary alterations.

Table 2—Bidirectional MR effects for HOMA-IR and lung function

Exposure	Outcome	SNPs (*n*)	β	95% CI	*P*
HOMA-IR	FEV_1	8	−0.13	−0.21 to −0.05	0.0018**
HOMA-IR	FVC	8	−0.11	−0.20 to −0.03	0.0080*
HOMA-IR	Tiffeneau	8	−0.04	−0.15 to 0.07	0.50
FEV_1	HOMA-IR	123	−0.04	−0.08 to 0.001	0.058
FVC	HOMA-IR	117	−0.05	−0.09 to −0.004	0.033*
Tiffeneau	HOMA-IR	125	−0.02	−0.06 to 0.01	0.23

Inverse variance–weighted estimates. *$P < 0.05$. **$P < 0.005$.

Peripheral Hyperinsulinemia

A possible direct role of insulin on the lung is suggested by both preclinical and clinical studies. In a rat model, insulin potentiated vagally induced bronchoconstriction via inhibition of M_2 receptors (31). Insulin was linked to proliferation, hypercontractile airway smooth muscle, and in a model of hyperinsulinemia in mice, insulin was shown to promote the deposition of collagen in the lung via activating the PI3/Akt–β-catenin axis that

promotes fibrosis (32). The use of inhaled insulin in clinical trials was associated with a reduction of FEV_1 and lung diffusion capacity for carbon monoxide, suggesting a direct action of insulin on lung (33). Additionally, a small clinical study in type 1 diabetes demonstrated a negative association between basal insulin doses and both FEV_1 and FVC, as well as with restrictive lung pattern (34). In the current study, the daily insulin dose was associated only with FEV_1, and not with FVC. A possible explanation is an impact of insulin on airway smooth muscle, which leads to airflow obstruction, a consecutively reduced FEV_1, and manifests more rapidly than structural changes in the lungs that could affect FVC (35).

Lung Function Across Diabetes Types

In contrast to one meta-analysis (8), this study found no differences in FEV_1 and FVC between T1D and CON. This could be due to the GDS cohort including individuals with recent-onset diabetes, while type 1 diabetes duration is longer in most studies included in the meta-analysis. Here, chronic alterations, such as enduring hyperglycemia and insulin resistance, could play a role in the observed impairment. Lower FEV_1 and FVC in type 2 diabetes compared with CON align with previous findings in a meta-analysis (9). The association between type 2 diabetes and reduced FEV_1 was still present after adjusting for all confounders that could affect pulmonary function. Key factors linked to these pulmonary function variables, such as insulin resistance and consequently hyperinsulinemia, likely emerge well before type 2 diabetes onset (36), while the metabolic precursor phase in type 1 diabetes is typically shorter. This extended exposure could explain the observed changes in recent-onset type 2 diabetes.

Lung Function Across Diabetes Subtypes

The finding of a lower FEV_1 and FVC in SIRD compared with CON and SAID aligns with the role of insulin resistance and the consequent increase in peripheral insulin levels in the link between diabetes and pulmonary function changes. Furthermore, pulmonary impairment could represent a further complication related to SIRD subtype that has been previously associated also with diabetic kidney disease and nonalcoholic fatty liver disease (20,21). While MARD has been initially thought to be a mild diabetes subtype not causing complications, our results highlight a clearly increased pulmonary risk compared with CON and SAID. Although the genetic link between subtypes and pulmonary impairment is unclear, a hypothesis could be that genetic and/or epigenetic factors may predispose both SIRD and MARD to lung alterations as demonstrated for the risk of renal and cardiovascular complications (37).

Role of Inflammation in the Link Between Glucose Metabolism Traits and Lung Function

In the whole study population, insulin sensitivity and clearance were associated with FEV_1 and FVC. A large cross-sectional study identified hs-CRP as a mediator of the relationship between diabetes and pulmonary function alterations (29). However, our data show that insulin resistance and clearance associate with lung function independent from inflammation, using the surrogates hs-CRP and WBC. This suggests that mechanisms beyond clinically detectable inflammation play a role in the connection between glucose metabolism and lung function.

Role of Skeletal Muscle in the Link Between Glucose Metabolism Traits and Lung Function

This study revealed that FFM, which predominantly represents skeletal muscle, was associated with both FEV_1 and FVC. Previous studies in both type 1 and type 2 diabetes have indicated reduced respiratory muscle strength and/or endurance in individuals with these conditions (15,16). Since the contraction of striated respiratory muscles is crucial for performing spirometry, impairment in these muscles could lead to reduced lung function parameters. Furthermore, dysfunctional skeletal muscle could affect insulin clearance and increase insulin levels since skeletal muscle is one of the sites of insulin uptake and degradation (38). Thus, this mechanism could explain a part of the association between insulin clearance and pulmonary function.

Clinical Impact of Pulmonary Alterations in Diabetes

The effects of diabetes on lung function may be especially important for individuals with pulmonary comorbidities, such as COPD and asthma, and could contribute to the substantial loss of life-years observed in those with both conditions (39). Furthermore, a longitudinal study showed that even early pulmonary alterations, such as preserved ratio impaired spirometry, a condition characterized by a normal Tiffeneau index and a reduced FEV_1, is associated with increased risk of adverse outcomes, including cardiovascular disease and all-cause mortality, in individuals with type 2 diabetes (40). This body of evidence highlights the great clinical relevance of preventing or at least early detecting pulmonary function changes in individuals with diabetes.

Study Strengths and Limitations

Using a comprehensive gold standard metabolic phenotyping of glucose metabolism, our study was able to precisely measure insulin sensitivity and insulin secretion both in type 1 and type 2 diabetes. These allowed us to study the association between pulmonary function and precise glucose metabolism traits. Furthermore, the findings in the GDS cohort were strengthened by an independent MR analysis. The exclusion of individuals with acute and/or severe illnesses improved the reliability of metabolic phenotyping and reduced the confounding factors in the analyses of the association between glucose metabolism traits and pulmonary function.

However, the data were generated in an ethnically nondiverse cohort, and individuals with extreme phenotypes of diabetes (e.g., very high glycemia) were not included. Although oral glucose-lowering medications were discontinued at least 3 days before the metabolic tests, we cannot fully exclude the impact of these medications on the metabolic phenotype. Ascertainment of pulmonary comorbidities could be biased by questionnaire assessment. Data about body plethysmography and diffusion capacity of the lungs for carbon monoxide were not available, neither was history of interstitial lung disease and acute respiratory exacerbations. However, individuals with acute and/or severe illnesses were excluded. The study design is cross-sectional; therefore, a longitudinal causal relationship between glucose metabolism traits and spirometry parameters within the GDS cannot be established. However, as the GDS is an ongoing study, the collection of follow-up data could enable future longitudinal analyses for the relationship between diabetes and pulmonary function.

Conclusion

This study emphasizes that individuals with type 2 diabetes, particularly those of the SIRD and MARD subtypes, show signs of early pulmonary alterations, even shortly after diagnosis and in those with well-controlled diabetes. Insulin sensitivity and clearance are key factors in this relationship, with hyperinsulinemia potentially contributing to lower FEV_1. Individuals with type 2 diabetes, especially the elderly and those with insulin resistance as well as individuals with type 1 diabetes who require high doses of exogenous insulin, could benefit from early screening and interventions focused on improving insulin sensitivity and reducing hyperinsulinemia to mitigate adverse pulmonary outcomes.

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